

REMARKS

Claims 1 and 19 are amended. Claims 1-8, 10, and 12-20 are pending. Favorable reconsideration is respectfully requested.

At the outset, Applicants thank Examiner Patterson for the helpful comments in the Outstanding Office Action to overcome the rejections therein. Further, Applicants thank Examiner Patterson for the brief helpful discussion of the present application over the telephone prior to filing this document.

The rejection of Claims 1-8, 10, and 1-20 under 35 U.S.C. § 112, first paragraph, and the new matter rejection is believed to be obviated by the above amendment combined with the remarks below.

The new matter rejection is believed to be obviated by the cancellation of the phrase "carbamoyl racemase". Accordingly, withdrawal of this ground of rejection is respectfully requested.

Applicants thank Examiner Patterson for indicating that the 112, first paragraph, rejection, may be obviated if Applicants directed the Examiner's attention to disclosures of JM 109, pOM22, and pOM21 because "the Examiner does not readily find this disclosure in the instant patent" (i.e., WO 00/58499). Applicants respectfully direct the Examiner's attention to page 10, line 23, of WO 00/58499 (WO '499), which specifically discloses *E. coli* JM109. Further, the Examiner's attention is directed to page 14, lines 14-15, of WO '499, which specifically discloses pOM22 and pOM21. Therefore, in accordance with the Examiner's suggestion, Applicants have pointed out specifically where JM109, pOM22, and pOM21 is specifically disclosed in WO '499.

In addition, the Examiner indicates that "the Examiner will consider whether to consider the data disclosed on page 7 as related to formula II" if Applicants can show that the structure of formula II is the "DL-allysine hydantoin" recited on page 7. In accordance with the Examiner's instructions, the following remarks are submitted to support Applicants' contention that the Examiner should consider the data disclosed on page 7 as related to formula II.

First, page 3, lines 5-10 of the present specification discloses that the present invention comprises the preparation of allysine acetal of the general formula I. Further, the present specification discloses at page 3, lines 10-15 that the starting material in the preparation of the allysine acetal of general formula I is a hydantoin of the general formula II, which has an acetal moiety. Still further, the present specification discloses at page 4, lines 16-17, that "the structures of the compound shown in formula (I) and (II) above relate to both optical isomers."

In light of the above, it is clear that formula II relates to "both optical isomers" which are D- and L-hydantoins. Further, the present process relates to preparation of allysine acetal of general formula I. Applicants respectfully submit the attached pages from the basic introductory organic textbook from Ralph J. Fessenden and Joan S. Fessenden entitled "Fessenden & Fessenden" (4th Edition) published by Brooks/Cole Publishing Co., copyright 1990 (see enclosed copies of cover and page 542-545). At page 542-545 of Fessenden & Fessenden attached hereto, it is demonstrated that a skilled artisan with basic organic chemistry knowledge understands what an acetal moiety would be and therefore demonstrates that the skilled artisan would understand what an allysine acetal structure entails. Moreover, Applicants specifically disclose at page 7, line 19, of the specification a result in the examples that is the production of L-allysine acetal of greater than 85% having a an optical purity of

greater than 99% enantiomeric excess. Accordingly, the skilled artisan would clearly understand that the "DL-allysine hydantoin" utilized in the example contains the acetal moiety and therefore falls within formula II. There is no other possible source of the acetal moiety on the resultant L-allysine acetal product.

In addition, the Examiner indicates that the Applicants has not addressed what is meant by "N-carbamoyl amino acid". Applicants respectfully submit that this issue was not addressed because it appeared as if the Examiner understood this phrase, more specifically the compound, in light of the results of the interview held January 23, 2003. Moreover, Applicants respectfully apologize for not addressing this issue more thoroughly. Regarding this issue, Applicants respectfully direct the Examiner's attention to Syldatk et al. (1988) Ann. N.Y. Acad. Sci. 542, 323-329 which was cited in the Examiner's PTO-892 form and enclosed with the Examiner's Office Action dated November 27, 2002. The Examiner relied on this reference in order to provide a 103 rejection which has now been withdrawn. Although Applicants respectfully thank the Examiner for withdrawing the 103 rejection in light of Applicants' arguments in the last response, Applicants once again direct the Examiner's attention to page 323 of this reference which specifically discloses a structure of a D- or L-carbamoyl amino acid. Accordingly, it appears as if the skilled artisan and the Examiner would clearly understand what an N-carbamoyl amino acid represents. Of course, the "N" of N-carbamoyl amino acid is generic and can represent either of the optical isomers D or L.

In light of the above, Applicants respectfully submit that Applicants have addressed all of the Examiner's questions related to both the new matter rejections and the 112, first paragraph, rejections. More specifically, Applicants have demonstrated that support is found in WO '499. Further, Applicants have demonstrated that formula II is a hydantoin that envelopes the "DL-allysine hydantoin" recited on page 7. Moreover, Applicants have

demonstrated that the skilled artisan would completely understand what a N-carbamoyl amino acid entails. Finally, Applicants demonstrate on page 7 that the *E. coli* cell strain that is utilized in the experiment is fully defined at page 5, line 26, of the present specification and within the previously provided WO '499 reference discussed above.

For all of the above reasons, the Applicants respectfully request withdrawal of the new matter and 112 rejections.

Applicants respectfully submit that the present application is now in condition for allowance. Should anything further be required to place this application in condition for allowance, the Examiner is requested to contact Applicants attorney by telephone.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT P.C.



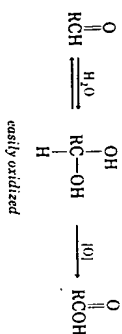
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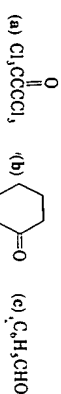


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**Study Problem**

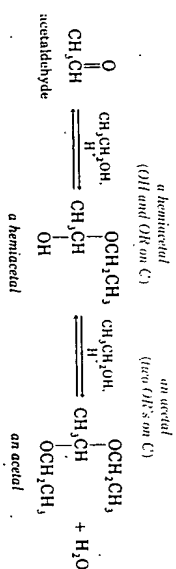
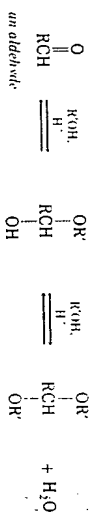
13.3 Which of the following compounds would you predict to form stable hydrates? Explain.

**B. Reaction with Alcohols**

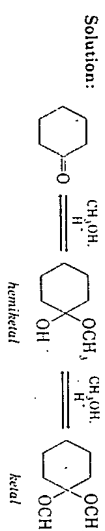
Like water, an alcohol can add to a carbonyl group. In most cases, the equilibrium lies on the aldehyde or ketone side of the equation, just as in the reaction with water.

The product of addition of one molecule of an alcohol to an aldehyde is called a **hemiacetal**, while the product of addition of two molecules of alcohol (with the loss of H_2O) is called an **acetal**. (Hemiketal and ketal are the corresponding terms used for ketone products.) All these reactions are catalyzed by a trace of strong acid.

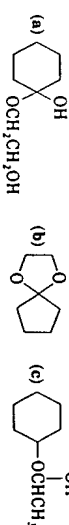
General:

**Sample Problem**

Give the structures of the organic compounds present in a methanol solution of cyclohexanone that contains a trace of HCl .

**Study Problems**

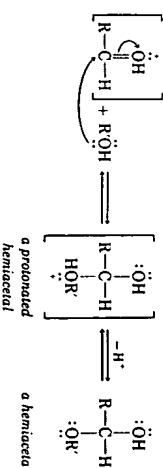
13.4 Which of the following structures contains a hemiacetal or ketal group, and which contains an acetal or ketal group? Circle and identify each group.



13.5 Give the structures of the alcohol and the aldehyde or ketone that are needed to prepare each of the compounds shown in the preceding problem.

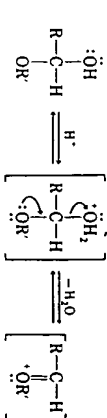
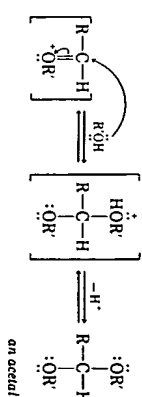
The mechanism for the reversible reaction of an aldehyde or a ketone with an alcohol is typical of the mechanisms for many acid-catalyzed addition reactions of carbonyl compounds: a series of protonations and deprotonations of oxygen-containing groups.

Protonation:

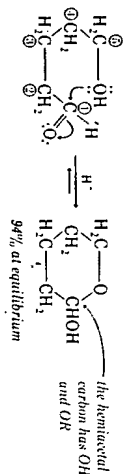
Attack of ROH :

In the mechanism for acetal formation from the hemiacetal, again protonation and deprotonation, along with loss of water, are the major reaction steps. Acetal formation from a hemiacetal is therefore a two-step substitution of an OR group for an OH group.

Protonation and loss of water:

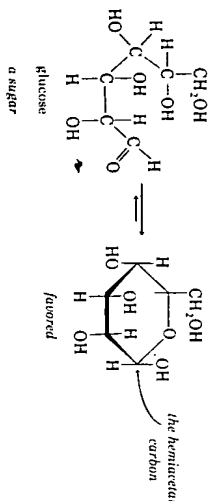
Attack of ROH :

In the equilibrium between an aldehyde, a hemiacetal, and an acetal, the aldehyde is generally favored. In an equilibrium mixture, we would usually find a large amount of aldehyde and only small amounts of hemiacetal and acetal. There is one important exception to this generality. A molecule that has an OH group γ or δ (1,4 or 1,5) to an aldehyde or ketone carbonyl group undergoes an intramolecular reaction to form a five- or six-membered hemiacetal ring. These cyclic hemiacetals are favored over the open-chain aldehyde forms.



94% at equilibrium

The reason that cyclic hemiacetals are important is that glucose and other sugars contain hydroxyl groups γ and δ to carbonyl groups. Sugars, therefore, form cyclic hemiacetals in water solution. This topic will be discussed in Section 22.4.



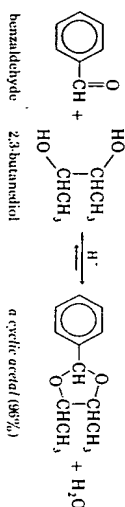
glucose
a sugar

favored

Study Problem

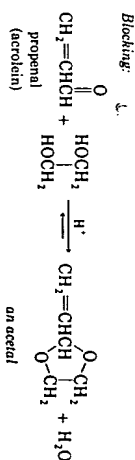
13.6 Predict the cyclic hemiacetal or hemiketal products in water solutions of (a) 5-hydroxy-2-hexanone, and (b) 1,3,4,5,6-pentahydroxy-2-hexanone. [One stereoisomer of (b) is *fructose*, or *fruit sugar*.]

In most cases, a hemiacetal cannot be isolated. Acetals, however, are stable in nonacidic solution and can be isolated. (In acidic solution, of course, they are in equilibrium with their aldehydes.) If an acetal is the desired product from reaction of an aldehyde and an alcohol, an excess of alcohol is used to drive the series of reaction steps to that product. Removing water as it is formed also helps drive the reversible reactions to the acetal. Best results in this type of reaction are obtained when the acetal is cyclic:

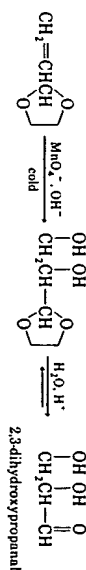


If a desired reaction can be carried out under alkaline conditions, acetal and ketal groups are effective blocking groups for aldehydes and ketones. For

example, after changing an aldehyde group to an acetal, we can oxidize a double bond in the same molecule without oxidizing the aldehyde to a carboxylic acid.



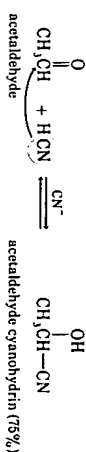
Oxidation of double bond and regeneration of aldehyde:



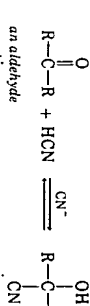
C. Reaction with Hydrogen Cyanide

Hydrogen cyanide (bp 26°) can be considered to be either a gas or a liquid with a low boiling point. In typical laboratory operations, it is used as a gas, but with a special apparatus it can be used as a liquid (and, in some cases, even as a solvent). Often, HCN is generated directly in a reaction mixture from KCN or NaCN and a strong acid. Hydrogen cyanide is toxic and is particularly insidious because some people can detect its odor only at levels that may be lethal.

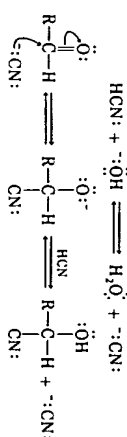
Like water and alcohols, hydrogen cyanide can add to the carbonyl group of an aldehyde or a ketone. The product in either case is referred to as a **cyanohydrin**.



General:



Hydrogen cyanide does not add directly to a carbonyl group. Successful addition requires slightly alkaline reaction conditions such as those found in a NaCN-HCN buffer solution. In alkaline solution, the concentration of cyanide ion is increased, and addition proceeds by nucleophilic attack of CN^- on the carbonyl group. Although weak nucleophiles (such as H_2O and ROH) require acid catalysis for addition to the carbonyl group, the strongly nucleophilic CN^- does not require a catalyst.



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EDITION

Organic Chemistry

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